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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,517	CLARKE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,32-40 and 184-198* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30, 32-40, and 184-198* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I without traverse in Paper No. 9 is acknowledged. Although no formal request on record has been made to cancel claims 31 and 41-183, applicants indicated in paper No. 9 that upon election, claims 1-30, 32-40, and 184-198 are pending, and in the marked-up copy of the claims, claims 31, and 41-183 have been indicated as canceled. Therefore, these claims have been treated as being canceled. Confirmation is required in response to this Office action. Claims 1-5, 7, 8, 15, 17, 23, 25, 26, 37, 39, 40 have been amended. Claims 184-198 are newly submitted.

Claims 1-30, 32-40, and 184-198 are pending and under current examination.

Priority

This application claims the benefit of priority from U.S. provisional applications 60/222,794 and 60/240,317, filed 8/3/2000 and 10/13/2000, respectively.

Drawings

This application contains color drawing or color photographs. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color

drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Specification

The abstract of the disclosure is objected to because it is lengthy. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

Claim Objections

Claim 12 is objected to because the use of the verbs ("is" and "provides") before "a detectable signal".

Claims 15-17 are objected to because they fail to further limit a previous claim. These claims are drawn to a process of introducing a solid tumor stem cell into an animal; they fail to further limit the cell. It is noted that the subject matter drawn to a

method of introducing the cell to a mammal or a chimeric animal is not the elected invention. Upon election of an invention for examination in this application, the claims should be amended so that they read on the elected invention.

Claim 32 is objected to because the word "either" in line 5 does not link two equally comparable subjects.

Claim 38 is objected to because the second "is" in line 1 should be deleted.

Claim 39 is objected to because the first "either" in line 3 does not link two equally comparable subjects, and it is redundant to use the word "either" twice in the context of the claims.

Claims 189-193 are objected to because they fail to further limit a previous claim. These claims are drawn to animals, which do not further define the characteristics of a solid tumor stem cell.

Claim 198 is objected to because it is a duplication of claim 188. Applicant is advised that should claim 188 be found allowable, claim 198 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-40, 188, and 198 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims are drawn to a method for enriching a population of cells for solid tumor stem cells (STSC) comprising contacting at least one reagent with a cell suspension derived from a solid tumor, wherein the reagent selectively binds to either a positive or a negative marker for tumor stem cells. Given the broadest reasonable interpretation, the claims embrace *a genus of markers* that positively or negatively identify a (any) solid tumor stem cell in a selective manner. The specification teaches advantages of identifying tumor stem cells according to instantly claimed invention,

however, the disclosed markers having such selective identifying power are limited to a combination of B38.1^{+} CD44+ CD24$^{-/low}$ lineage^{-} for breast carcinoma cells (e.g. paragraph 82). In working examples, the specification teaches that all B38.1^{+} CD44+ CD24$^{-/low}$, but none of the B38.1^{+} CD44+ CD24^{+} breast cancer cells form tumors upon introduced *in vivo* (example 7 and table 6). In working example 19 and 20, the specification teaches that B38.1^{+} CD44+ CD24$^{-/low}$ lineage^{-} population could also be seen in ovarian carcinoma and two lines of sarcoma. However, the specification fails to teach the tumor-forming ability of the ovarian and sarcoma cells having the phenotype B38.1^{+} CD44+ CD24$^{-/low}$ lineage^{-}; the specification fails to disclose *any other* markers besides the combination B38.1^{+} CD44+ CD24$^{-/low}$ lineage^{-} that identify a tumor stem cell, whether the characteristic for breast and ovarian carcinoma would apply to any solid tumor stem cell, such as none epithelial origin considering that B38.1^{+} is known as a marker for breast epithelial cancer. The specification fails to set forth in terms of distinguishing characteristics for the genus of markers and/or combination of markers for selectively identifying *any* and *all* solid tumor stem cells. The skilled artisan cannot envision the detailed chemical structure of all markers encompassed by the claims, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

An adequate written description for a STSC identifying marker requires more than a mere statement that it is part of the invention, what is required is a description of the marker itself. It is not sufficient to define marker solely by its principal biological property, i.e. a solid tumor stem cell positive marker or negative marker, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any marker with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all markers that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific markers that are positive or negative on the surface of any and all solid tumor stem cells, which provide the means for practicing the invention.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the specification does not provide an adequate written description of the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of

the claimed invention. Therefore, only the B38.1^{+} CD44+ CD24$^{-/low}$ lineage^{-} combination marker meets written description requirement for identifying the stem cells of breast epithelial cancers (breast carcinoma).

Claims 32-40, 188, and 198 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enriching tumor stem cells for breast carcinoma by identifying and isolating a B38.1^{+} CD44+ CD24$^{-/low}$ lineage^{-} cell population, does not reasonably provide enablement for enriching any solid tumor stem cells using any combination of the genus of positive and negative markers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention without undue experimentation.

As discussed in the immediate preceding section, the specification fails to provide an adequate written description for the genus of markers that may positively or negatively identifying any and all solid tumor stem cells, thus, except for the B38.1^{+} CD44+ CD24$^{-/low}$ lineage^{-} breast cancer cells, the skilled artisan intending to practice the invention have to first carry out extensive experimentation to determine which marker or combination of markers would identify a particular type of tumor stem cells. Accordingly, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

Moreover, claims 3, 4, 6, 26, 37, and 187 are drawn to a solid tumor stem cell lacking detectable levels of certain CD lineage markers (CD2, CD3, CD10, CD14, CD16, CD31, CD45, CD64, and CD140) and a method of enriching the solid tumor stem cell by negative selection with LINEAGE markers selected from the group of recited above, and cells selected by the process. The claims embrace a selection process for any solid tumor stem cells of any cell origin (lineage), but *Janeway, Jr. et al* teaches that the lineage markers recited in these claims are for the hematopoietic lineage cells (Immunobiology, Appendix I), thus, they would not normally present in cells of other lineages, such as breast cancer cells. The specification fails to teach whether these lineage markers are selective for STSC but not *non*-tumorigenic cells of *any* solid tumor, i.e. selectively identify STSC, thus, the selection process dose not appear to be enabled or applicable to any tumor type for enrichment in the absence of evidence to the contrary.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7, 8, 15-19, 187, and 189-193 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-17 and 189-193 are vague and indefinite because they are drawn to a process of introducing solid tumor stem cells to an animal and the characteristics of the animal, but depend from a claim drawn to a tumor stem cell, it is unclear whether applicants intend to claim the isolated solid tumor stem cells or a chimeric animal or a process of introducing the cells to a mammal.

Claim 18 is vague and indefinite because it recites that the isolated tumor stem cell "further comprising a culture medium", which reads on that the cell contains culture medium within the cell membrane, and at the same time it also situated in the culture medium. It is unclear the relative location of the cell and the medium, thus, the metes and bounds of the claims are unclear. Further, the recitation is also contrary to the common knowledge of cell biology because a vigorous proliferating cell could situate in a culture medium but would not allow the culture medium to enter the cell membrane. For purpose of compact prosecution, the claim would be interpreted as a composition comprising a solid tumor stem cell and a culture medium.

Claim 187 recites the limitation "the lineage markers" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-8, 15-18, 20, 21, and 189-193 are rejected under 35 U.S.C. 102(b) as being anticipated by *Salmon et al* (New Eng J Med 1978;298:1321-7) and as evidenced by *Janeway, Jr. et al* (Immunobiology, 1999) and *Hartman et al* (Int J Cancer 1999;82:256-67).

The claims are drawn to an isolated solid tumor stem cell derived from a solid tumor and is tumorigenic, wherein said cell does not express detectable levels of CD2, CD3, CD10, CD14, CD16, CD31, CD45, CD64, and CD140, wherein said cell is an epithelial cancer, expressing epithelial specific antigen (ESA), preferably ovarian cancer, wherein said stem cell is situated in culture medium or affixed to a substrate, wherein said stem cell has been treated to reduce proliferation.

Salmon et al disclose a solid tumor stem cell (table I) derived from the ovarian carcinoma (malignant ovarian epithelial cells), situated in a culture medium or affixed to 3% agar substrate (sections in page 1322), and gave rise to new tumor cell colonies (tumorigenic). While not relied upon, *Janeway, Jr. et al* teach the recited CD markers are expressed in blood cells or endothelial cells (Appendix I), thus, the disclosed ovarian epithelial tumor stem cells would intrinsically lack detectable levels of

expression of these markers. Likewise, *Hartman et al* teach that ovarian epithelial cancer cells (carcinoma) express epithelial specific antigen (1st paragraph, page 256), the disclosed ovarian epithelial tumor stem cells would intrinsically express ESA. *Salmon et al* also teach that tumor stem cells are tumorigenic and would form new tumor *in vivo* (2nd paragraph, page 1321). They go on to treat the tumor stem cells with drugs that inhibit cell growth (e.g. figure 1). Therefore, *Salmon et al* anticipate the instant claims.

Please note that claim recitation, "the solid tumor stem cell is introduced into a host animal", or "wherein the animal is a mammal" has not been given patentable weight in this rejection and rejections that follow because it merely recites the intended use of the cells. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 1, 3-8, 15-18, 20, 22, and 189-193 are rejected under 35 U.S.C. 102(b) as being anticipated by *Salmon et al* (US 4,411,990, IDS/A1).

Claim 22 is drawn to that the solid tumor stem cell has been treated to increase proliferation.

Salmon et al disclose tumor stem cells derived from various solid tumors, including ovarian and lung carcinomas (table I), which are situated in a culture medium or affixed to an agar substrate (column 3, lines 15-58). These cells are epithelial tumors,

thus, would intrinsically express ESA and lack the expression of CD2, CD3, CD10, CD14, CD16, CD31, CD45, CD64, and CD140. *Salmon et al* also teach adding nutrients such as METGF to culture system to promote stem cell colony growth (column 4, lines 35-60), and that tumor stem cells are tumorigenic and would form new tumor in vivo (column 1, line 23). Therefore, *Salmon et al* anticipate the instant claims.

Claims 1-8, 15-18, 23-29, 184-187, and 189-197 are rejected under 35 U.S.C. 102(b) as being anticipated by *Martin et al* (Exp Hematol 1998;26:252-64), and as evidenced by *Schlom et al* (US 4,612,282).

The claims are drawn to an isolated solid tumor stem cell as well as an enriched population of said stem cell, derived from a solid tumor and is tumorigenic, wherein said stem cell expresses CD44, but not detectable levels of CD2, CD3, CD10, CD14, CD16, CD31, CD45, CD64, and CD140b, wherein said stem cell is an epithelial cancer, expressing ESA, preferably breast cancer, wherein said stem cell is situated in culture medium.

Martin et al teach an enriched population of metastatic tumor cells derived from breast cancer epithelial cells, wherein the tumor cells were situated in a culture medium after collection, and were 25-fold enriched than the original collected tumor cells (abstract), wherein the cell population were negative for CD45 (right column, page 253), wherein about 4% of the cells in the enriched population express CD44v6 (section in page 257). They go on to teach that such result is consistent with the previous study in animal models "SHOWING THAT ONLY A SMALL PERCENTAGE OF THE CIRCULATING TUMOR CELLS IS

ABLE TO SUCCESSFULLY INITIATE METASTATIC COLONIES" (i.e. tumor stem cells, last paragraph, page 262). The disclosed breast epithelial tumor stem cells express ESA (cytokeratin-8), and lack detectable levels of expression of CD2, CD3, CD10, CD14, CD16, CD31, CD45, CD64, and CD140b. While not relied upon, *Schlom et al* teach that B38.1 intensely expressed in mammary carcinoma (breast epithelial cancer, table I), possess a "pancarcinoma" pattern of binding activity (column 7, lines 2-4), and could be used for diagnosis of primary and metastatic breast tumor (column 10, line 1-51). Thus, the tumor stem cells taught by *Martin et al* would intrinsically express B38.1.

Please note claim recitation "wherein the solid tumor stem cell expresses lower levels of the marker CD24" (Claims 186 and 197) describes an inherent property of a tumor stem cell. Claims 186 and 197 are included in this rejection because *Martin et al* disclose the same type of tumor stem cells as disclosed in the instant specification, i.e. derived from breast epithelial tumor, expressing CD44 marker and ESA, negative in CD45 marker, and were tumorigenic (metastasis), therefore, these cells would also express lower levels of the marker CD24 than mean expression of CD24 by non-tumorigenic cancer cells.

Accordingly, *Martin et al* anticipate instant claims.

Claims 1, 3-7, 9-13, 15-18, 184, and 189-193 are rejected under 35 U.S.C. 102(b) as being anticipated by *Nierodzik et al* (Blood 1998;92:3694-3700).

Claims 9-13 are drawn to an isolated solid tumor stem cell contains a polynucleotide vector, preferably a plasmid, a reporter polynucleotide, and a recombinant polynucleotide.

Nierodzik et al teach an isolated population of tumor cells derived from colon carcinoma and melanoma and having a pulmonary metastatic phenotype (abstract), thus, they are solid tumor stem cells (tumorigenic). The disclosed colon epithelial tumor stem cells intrinsically express ESA and lack detectable levels of expression of CD2, CD3, CD10, CD14, CD16, CD31, CD45, CD64, and CD140b. The solid tumor stem cells are further transfected with an expression vector (pCDNA3) encoding a thrombin receptor (recombinant polynucleotide), and containing a reporter gene (Geneticin resistance with G418, see 1st paragraph, page 3695).

Accordingly, *Nierodzik et al* anticipate the instant claims.

Claims 1, 3, 4, 6, 9-18, and 189-193 are rejected under 35 U.S.C. 102(b) as being anticipated by *Bromberg et al* (PNAS 1995;92:8205-9).

Claim 14 requires that the recombinant polynucleotide be integrated into a chromosome of the solid tumor stem cell.

Bromberg et al teach an isolated tumor stem cell derived from melanoma, transfected with a retroviral vector encoding a mutant extracellular TF, and its tumorigenic ability was tested by introducing the transfected cells in SCID mice (abstract). The melanoma stem cells would not express CD2, CD3, CD10, CD14, CD16,

CD31, CD45, CD64, and CD140b. Accordingly, *Bromberg et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 30, 32-40, 188, and 198 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Martin et al* (Exp Hematol 1998;26:252-64), in view of *Salmon et al* (US 4,411,990, IDS/A1).

Claims 32-40, 188, and 198 are drawn to a method for enriching a population of cells for solid tumor stem cells comprising (a) dissociating a solid tumor to form a cell suspension, (b) contacting the dissociated cells with at least one reagent that selectively

binds to a positive marker for a solid tumor stem cell, or a combination of reagents that selectively bind either a positive or a negative marker for a solid tumor stem cell, (c) selecting cells that bind to the positive marker/or do not bind to the negative marker, and (d) isolating the selected solid tumor stem cell; wherein the solid tumor is a sarcoma or epithelial cancer, preferably a breast cancer, wherein the selection is performed by flow cytometry, FACS, and/or magnetic selection, wherein the reagent is an antibody, wherein the reagent is conjugated to a fluorochrome or to magnetic particles, wherein the positive marker is an epithelial specific antigen.

Martin et al teach a method for enriching the metastatic breast cancer cells in the bone marrow comprising contacting isolated cells with an antibody against an epithelial specific antigen (cytokeratin-8) conjugated to magnetic particles as positive selection marker, and an anti-CD45 antibody conjugated to a fluorochrome (CyChrome) as a negative marker (see particularly sections in right column, page 253-left column, page 254) and isolating the selected cells (steps b-d). About 4% of the isolated tumor cells are CD44+ (right column, page 257). *Martin et al* enrich the metastatic breast cancer cells in the bone marrow, thus, no need for dissociating a solid tumor (step a).

However, the step a is well known in the art long before the effective filing date of the instant application. For example, *Salmon et al* teach that before assaying for solid tumor stem cells from primary or metastatic human tumors, the biopsy sample should be first subject to a fractionation treatment (dissociating a solid tumor) using suitable fractioning techniques known in the art (column 5, lines 15-29).

Claim 30 is drawn to a tumor cell population that is at least 50-fold enriched, *Martin et al* teach a tumor cell population that is 25-fold enriched, not 50-fold enriched, however, this could be achieved by repeating the steps (b) through (d).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method steps taught by *Salmon et al, and Martin et al*, for enriching breast cancer stem cells with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because if the tumor sample is from a solid tumor, the cells have to be dissociated before they could contact an antibody for enrichment. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Salmon et al* (US 4,411,990, IDS/A1), in view of *Jeffries et al* (Mol Cell Bio 2000 Jun;20:3928-41).

Claim 19 is drawn to a culture medium for the solid tumor stem cell comprises a Notch ligand.

Salmon et al disclose adding nutrients such as METGF to culture system to promote stem cell colony growth (column 4, lines 35-60), but fail to teach adding a Notch ligand in the culture system.

Jeffries et al teach that Notch proteins are cell surface receptors, and the interaction between Notch and its proposed ligand initiating a signaling cascade that

governs cell fate decisions (1st paragraph, page 3928), that such interaction has a direct role in the transformation of cells and can cooperate with cellular proto-oncogenes to accelerate tumorigenesis in different tissue types (see particularly 3rd & 4th paragraph in page 3928).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Salmon et al,* by simply adding Notch ligand to the culture medium for culturing tumor stem cells with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it would enhance the tumorigenecity of STSC. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Patent Examiner
Art Unit 1632

QL
February 24, 2003